R EMARKS

Regarding the rejection based on the finding of indefiniteness

Claims 1, 6 –9 and 11 were rejected on the basis that the variables R_5 and X co not appear anywhere in the claimed *formulas*. This ground of the rejection is respectfully submitted to be in serious error.

There is no requirement in patent law or practice (including the rules of practice and the M.P.E.P) that would require all variables to appear in the *structural formulas*. The requirement is only that the variables be properly defined in the claims. The claims comply with this requirement. In order to facilitate the present explanation the pages where the claims appear in this amendment were provided with line numbers in the left margin. Thus, in Claim 1 R_5 is defined as a "subgroup" or substituent of $\mathbf{R_1}$ and $\mathbf{R_2}$ on page 5, lines 9 –12 and again on page 6, line1. In Claim 11 R_5 is defined as a "subgroup" or substituent of $\mathbf{R_1}$ and $\mathbf{R_2}$ on page 9, lines 1 –4 and again on line 15 of page 9.

In Claim 1 the variable X is defined as a "subgroup" or substituent of $\mathbf{R_1}$ and $\mathbf{R_2}$ on page 5, lines 9 - 17. In Claim 11 X is defined as a "subgroup" or substituent of $\mathbf{R_1}$ and $\mathbf{R_2}$ on lines 1 – 9 of page 9. These variables in the independent claims provide proper antecedent basis for Claims 6 – 9.

The Examiner's helpful suggestion to change the expression "at least" into "one or more" is gratefully acknowledged and has been implemented (where applicable) in the claims. The term "includes" was changed to "has" (where applicable) and in Claim 20 the misspelling of the word "relative" was corrected.

The definition of the variable Y was deleted in Claim 1 because, as a result of the requirement for restriction and applicant's subsequent election, the Y group is no longer pertinent to the present claims.

The undesigned attorney noted that claim 9 appeared twice. This misnumbering of the claims was corrected by canceling the second erroneous occurrence of Claim 9, and by presenting its subject matter as "new" claim 34.

Regarding new claims 35 and 36

Independent Claim 35 is drawn to **Compound 9** of the specification which was the elected species in response to the previous requirement for election of species. Claim 35 replaces previous Claim 28, now cancelled, which was drawn to the same compound but depended on Claim 21.

Claim 36 is drawn to **Compound 27** of the specification. This compound is disclosed *inter alia* on pages 117 – 119 of the specification.

The obviousness-type double patenting rejection is in error

The obviousness-type double patenting rejection is respectfully traversed as having been made in error. The reasons are as follows:

In the Office Action Claims 1 –10 of United States Patent No. 6,093,734 were held to render obvious the claims of the present application. All claims of the present application are drawn to prodrugs of proton pump inhibitors which include a substituted sulphonyl moiety attached to one of the nitrogens of the benzimidazole moiety where the substituted sulphonyl moiety itself carries an acidic function, namely a carboxylic acid (or a tetrazole moiety) that is present either as the free acid or as pharmaceutically acceptable salt of the free acid. For the sake of simplicity of illustration and for the purposes of these Remarks only, the sulphonyl moiety attached to the benzimidazole nitrogen is depicted as

$(HOOC)_n$-R- SO_2- benzimidazole

As the application amply explains, cleavage of the above-noted substituted sulphonyl moiety gives rise to the proton pump inhibitory (PPI) drugs which are specified by formula in the application and claims.

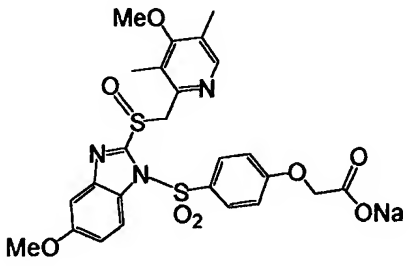
None of the claims (or specification) of United States Patent No. 6,093,734 include a carboxylic acid (or tetrazole) group in the substituted sulphonyl moiety that is attached to the benzimidazole nitrogen of a PPI drug. In this regard the Examiner's attention is respectfully directed to the Summary of the Invention in the cited patent, and particularly to groups R_{21} and R_{17} which define the substituents of the sulphonyl group.

The presence of the acidic function in the substituted sulphonyl moiety is an important feature of the compounds of the present invention which provides significant advantages over the prior art PPIs and prodrugs of PPIs including the subject matter of the cited claims. As the application itself states "a disadvantage of many of the presently used proton pump inhibitors is that for therapy by injection in a liquid form they must be reconstituted from a lyophilized powder in a medium having the high pH of approximately 9.5 to 10.5. The prodrugs of the present invention overcome the disadvantage of requiring a reconstituting medium having such high pH, because the compounds of the present invention can be reconstituted to form an injectable liquid in a medium of approximately pH 7 to 8." (see page 33 of this case.)

"A further significant advantage of the proton pump inhibitor prodrugs of the present invention relative to the proton pump inhibitor prodrugs disclosed and claimed in United States Patent No. 6,093,734 is their **increased solubility**. To illustrate this, the aqueous solubility of each of the prior art compounds (a) through (f) shown below is less than 0.01 μg per milliliter (<0.01μg/mL) when these prior art compounds are prodrugs

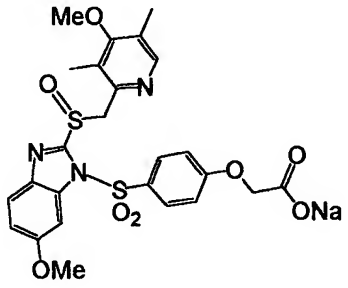
of the drug LANSOPRAZOLE (compounds (a) through (c), and between 5 to 8 μg per milliliter (5 to 8 μg/mL) when these prior art compounds are prodrugs of the drug OMEPRAZOLE (compounds (d) through (f). In contrast, the solubility in distilled water of the free carboxylic acids of **Compounds 2** and **9** of the invention is greater than 100 μg per milliliter (>100 μg/mL)." (For the just quoted text from the application and for the structures showing the prior art less soluble and the exemplary more soluble compounds of the invention, see pages 35 through 39 of the specification.

Still more data regarding solubility of an exemplary compound of the present invention, the isomeric structures of which are shown below, and which have compound numbers **9** and **10** in the application (see page 75) are shown in the Table 1 below.



Compound 9

+



Compound 10

Table 1. Solubility Profile of Compounds 9 and 10 at 25 °C in Buffered Aqueous Solutions

pH	Buffer Composition	Solubility (mg/mL)
1	0.1 M HCl	1.8
3	Citric Acid (0.1 M)/ Na_2HPO_4 (0.2 M)	0.4
5	Citric Acid (0.1 M) /Na_2HPO_4 (0.2 M)	>50
7	sodium phosphate (0.1 - 0.2 M)	>50

9	sodium phosphate (0.1 - 0.2 M)	>50

It can be seen that this compound is quite soluble in a neutral pH range. It is well known that this type of solubility is desirable and advantageous for use as a drug.

Additional data regarding the stability of the exemplary isomeric compounds **9** and **10** in aqueous solutions at several pH values are provided in Table 2 below.

Table 2. Stability Profile of Isomeric Compound **9** and **10** at 25 °C in Buffered Aqueous Solutions

PH	Buffer Composition	Half-life ($t_{1/2}$) hours	Shelf life ($t_{90\%}$) hours	Degradation Rate Constant (k) 1/hours
1	0.1 M HCl	3.6	0.5	0.194
3	Citric Acid (0.1 M)/ Na_2HPO_4 (0.2 M)	78.0	11.9	0.009
5	Citric Acid (0.1 M) /Na_2HPO_4 (0.2 M)	89.2	13.6	0.008
7	sodium phosphate (0.1 - 0.2 M)	286.8	43.6	0.002
7.4	sodium phosphate (0.1 - 0.2 M)	291.2	44.3	0.002
9	sodium phosphate (0.1 - 0.2 M)	23.0	3.5	0.030
10	sodium phosphate (0.1 - 0.2 M)	2.3	0.4	0.298

The results in **Table 2** unexpectedly show that, in contrast to the conventional proton pump inhibitors, the compounds of the invention are more stable in neutral and acidic solutions than they are at a higher pH. In the proper pH range, they are also significantly more stable than the current commercial proton pump inhibitors. In a neutral solution, the shelf-life of compound 1 is over forty hours. As low as around pH 3, compound 1 has a sufficient shelf life to be comparable to the commercial omeprazole intravenous formulation Losec®, which is reported by the manufacturer,

Astra Zeneca, to have a shelf life of "12 hours when dissolved in normal saline and 3 hours in 5% dextrose when stored at 25°C".

Thus, the prodrugs disclosed herein are both more stable and more flexible in terms of their use in acidic and neutral aqueous solutions as compared to the commercial proton pump inhibitor products currently available. This should allow bolus injection of the compounds disclosed herein as opposed to the slow infusion of the drug currently in practice because the present compositions will not have the irritation associated with the high pH traditionally used with proton pump inhibitors. This should also allow greater flexibility in co-administering these compounds with drugs which are unstable or otherwise incompatible with high pH.

It is well known in the art that conventional PPIs are acid-labile and not very stable in neutral or near-neutreal pH. The stability of omeprazole and other proton pump inhibitors have been reported (Kromer et al., "Differences in pH-Dependent Activation Rates of Substituted Benzimidazoles and Biological in vitro Correlates", Pharmacology 1998; 56:57-70; and Ekpe et al, "Effect of Various Salts on the Stability of Lansoprazole, Omeprazole, and Pantoprazole as Determined by High Performance Liquid Chromatograpy", Drug Development and Industrial Pharmacy, 25(9), 1057-1065 (1999)), and while the stability is somewhat buffer dependent, typical half-lives for omeprazole are about 40 hours at pH 7, which is nearly an order of magnitude shorter than the prodrug half-live presented in Table 2. These results again suggest that the compounds of disclosed herein can be injected at a more neutral pH than is currently possible with the currently available proton pump inhibitors.

Also for stability reasons for oral administration in most cases it is necessary to enterically coat the prior art PPI drugs (and prodrugs) in order

to prevent the acidic milieu of the stomach from destroying the drug before the drug is absorbed into systemic circulation. Thus, the increased stability in acid of the prodrugs of the present invention is a significant improvement in the art, and may very well eliminate or decrease the need for enteric coating.

In light of the foregoing the "holding of obviousness-type double patenting" is in error and should not be maintained. All claims are in *prima facie* allowable condition.

In the event the Examiner is of the opinion that a telephone conference with the undersigned attorney would materially facilitate the final disposition of this case, she is respectfully requested to telephone the undersigned attorney at the below listed telephone number.

Respectfully submitted

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